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EXAMINER	
HELMS, LARRY RONALD	
ART UNIT	PAPER NUMBER
1642	7

DATE MAILED: 08/05/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No. 09/925,140	Applicant(s) LAL ET AL.	
	Examiner Larry R. Helms	Art Unit 1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 May 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18,27 and 28* is/are pending in the application.

4a) Of the above claim(s) *1,2,8,10,13-18,27 and 28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7,9,11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Pri rity under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group II, claims 3-7, 9, 11, and 12, in Paper No. 6 is acknowledged. The traversal is on the ground(s) that "Groups V, VI, VIII, and IX (claims 13-15, 27, and 28) are drawn to methods of use of the polynucleotides of Group II, and should be examined together" and then the response cites In re Ochiai , In re Brouwer to rejoinder of process claims covering the same scope of product claims. In response to this the examiner acknowledges this and method claims with the same scope will be rejoined upon allowance of the product claims. The response further states that Group I has already been examined and allowed and Groups VII, IV, III should be examined together with the Group II claims (see page 6 of response). This is not persuasive. Applicant has provided no evidence to establish why the requirement for restriction is improper. In addition, as stated in the restriction requirement the products of proteins, polynucleotides, transgenic organism and antibody are all structurally and functionally distinct. In addition, as stated in the restriction requirement the methods of Groups V-IX differ in the method objectives and in the steps and reagents used and are distinct. As to the question of burden of search, classification of subject matter is merely one indication of the burdensome nature of the search involved. The literature search, particularly relevant in this art, is not co-extensive and is much more important in evaluating the burden of search. Clearly different searches and issues are involved in the examination of each group. For these reasons the restriction requirement is deemed to be proper and is made **FINAL**.

2. Claims 1-2, 8, 10, 13-18, 27-28 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions. Applicant timely traversed the restriction (election) requirement in Paper No. 6.

3. Claims 3-7, 9, 11, and 12 are under examination.

NOTE

The following papers have not been made part of the permanent records of the United States Patent and Trademark Office (Office) for this application (37 CFR 1.52(a)) because of damage from the United States Postal Service irradiation process:

Mailroom Stamp Date	Certificate of Mailing Date
5/24/02	5/9/02

The above-identified papers, however, were not so damaged as to preclude the USPTO from making a legible copy of such papers. Therefore, the Office has made a copy of these papers, substituted them for the originals in the file, and stamped that copy:

COPY OF PAPERS
ORIGINALLY FILED

If applicant wants to review the accuracy of the Office's copy of such papers, applicant may either inspect the application (37 CFR 1.14(d)) or may request a copy of the Office's records of such papers (*i.e.*, a copy of the copy made by the Office) from the Office of Public Records for the fee specified in 37 CFR 1.19(b)(4). Please do **not** call the Technology Center's Customer Service Center to inquiry about the completeness or accuracy of Office's copy of the above-identified papers, as the Technology Center's Customer Service Center will **not** be able to provide this service.

If applicant does not consider the Office's copy of such papers to be accurate, applicant must provide a copy of the above-identified papers (except for any U.S. or foreign patent documents submitted with the above-identified papers) with a statement that such copy is a complete and accurate copy of the originally submitted documents. If applicant provides such a copy of the above-identified papers and statement within **THREE MONTHS** of the mail date of this Office action, the Office will add the original mailroom date and use the copy provided by applicant as the permanent Office record of the above-identified papers in place of the copy made by the Office. Otherwise, the Office's copy will be used as the permanent Office record of the above-identified papers (*i.e.*, the Office will use the copy of the above-identified papers made by the Office for examination and all other purposes). This three-month period is not extendable.

Specification

4. The disclosure is objected to because of the following informalities:

a. The first line of the specification should be updated to indicate application 09/088,435 is now U.S. Patent 6,277,619.

Appropriate correction is required.

Claim Objections

5. Claims 3-7, 9 are objected to because of the following informalities: The claims are dependent on non-elected claims. Claims 3-7, 9 will be examined with all the limitations recited in the non-elected claims from which they depend.

Appropriate correction is required.

Claim Rejections - 35 USC § 101

6. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 3-7, 9, 11, and 12 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The claims are drawn to an isolated purified polynucleotide encoding a polypeptide comprising an amino acid sequence selected from SEQ ID No:1, a naturally occurring sequence that is at least 90% sequence identical to SEQ ID No:1, a biologically active fragment of SEQ ID No:1, an immunogenic fragment of SEQ ID No:1, and a polynucleotide encoding SEQ ID NO:2 an a promoter, a cell transformed with the

polynucleotide, a polynucleotide that comprises a naturally occurring polynucleotide that is 90% identical to SEQ ID NO:2 and complements thereof and a polynucleotide that is at least 60 contiguous nucleotides thereof. The specification contemplates a role for these compounds in the treatment/diagnosis of metabolic diseases and cancer (see pages 26 and 35). While the specification does disclose SEQ ID No. 1 and the polynucleotide SEQ ID NO:2, there is no objective evidence, either in the specification or in the prior art of record, which discloses or suggests that SEQ ID No. 1 or SEQ ID NO:2 plays a role in metabolic diseases or cancer. The specification only mentions that SEQ ID No. 1 has 56.7% identity with human liver serine dehydratase and also shares a potential casein kinase II phosphorylation site, two potential protein kinase C phosphorylation sites and that analysis of these sequences in various libraries shows 48% of these sequences are associated with cancer, 29% are involved with immune response, and 23% are fetal, cell proliferating (see page 14). On page 23, the specification suggests that the human serine dehydratase homolog appears to play a role in disorders of metabolism and cancer because the protein is expressed in tissues that are cancerous, proliferating, or involved in immune response. However, no data is presented.

The assertion that the disclosed polypeptides have biological activities similar to serine dehydratase enzymes is not credible in the absence of supporting evidence, because the relevant literature reports numerous examples of polypeptide families wherein individual members have distinct, and even opposite, biological activities. For example, Tischer et al. (U.S. Patent 5,194,596) establishes that VEGF (a member of the

PDGF, or platelet-derived growth factor, family) is mitogenic for vascular endothelial cells but not for vascular smooth muscle cells, which is opposite to the mitogenic activity of naturally occurring PDGF which is mitogenic for vascular smooth muscle cells but not for vascular endothelial cells (column 2, line 46 to column 3, line 2). The differences between PDGF and VEGF are also seen *in vivo*, wherein endothelial-pericyte associations in the eye are disrupted by intraocular administration of PDGF but accelerated by intraocular administration of VEGF (Benjamin et al., 1998, Development 125:1591-1598; see Abstract and pp. 1594-1596). Vukicevic et al. (1996, PNAS USA 93:9021-9026) disclose that OP-1, a member of the TGF-β family of proteins, has the ability to induce metanephrogenesis, whereas closely related TGF-β family members BMP-2 and TGF-β1 had no effect on metanephrogenesis under identical conditions (p. 9023, paragraph bridging columns 1-2). See also Massague, who reviews other members of the TGF-β family (1987, Cell 49:437-8, esp. p. 438, column 1, second full paragraph to the end). Similarly, PTH and PTHrP are two structurally closely related proteins which can have opposite effects on bone resorption (Pilbeam et al., 1993, Bone 14:717-720; see p. 717, second paragraph of Introduction). Finally, Kopchick et al. (U.S. Patent 5,350,836) disclose several antagonists of vertebrate growth hormone that differ from naturally occurring growth hormone by a single amino acid (column 2, lines 37-48).

Generally, the art acknowledges that function cannot be predicted based solely on structural similarity to a protein found in the sequence databases. For example, Skolnick et al. (2000, Trends in Biotech. 18:34-39) state that knowing the protein

structure by itself is insufficient to annotate a number of functional classes, and is also insufficient for annotating the specific details of protein function (see Box 2, p. 36). Similarly, Bork (2000, Genome Research 10:398-400) states that the error rate of functional annotations in the sequence database is considerable, making it even more difficult to infer correct function from a structural comparison of a new sequence with a sequence database (see especially p. 399). Such concerns are also echoed by Doerks et al. (1998, Trends in Genetics 14:248-250) who state that (1) functional information is only partially annotated in the database, ignoring multi functionality, resulting in underpredictions of functionality of a new protein and (2) overpredictions of functionality occur because structural similarity often does not necessarily coincide with functional similarity. Smith et al. (1997, Nature Biotechnology 15:1222-1223) remark that there are numerous cases in which proteins having very different functions share structural similarity due to evolution from a common ancestral gene. Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts. Finally, Bowie et al. (1990, Science 247:1306-1310) state that determination of three dimensional structure from primary

amino acid sequence, and the subsequent inference of detailed aspects of function from structure is extremely complex and unlikely to be solved in the near future (p. 1306). Thus, the specification fails to support the asserted credible, specific and substantial utility of growth factor activity.

The specification does not support a credible, specific and substantial utility regarding the claimed polynucleotides encoding SDHH and variants thereof for purposes unrelated to the asserted biological activity. For example, the specification asserts that the claimed polynucleotides are involved in metabolic disorders and cancer based solely on the structural similarity between SDHH and SDH. The specification does not disclose a correlation between any specific disorder and an altered level or form of the claimed polynucleotides. Also, the specification does not predict whether the claimed polynucleotides would be overexpressed or underexpressed in a specific, diseased tissue compared to the healthy tissue control.

There is no correlation between this suggested use and metabolic diseases or cancer. Thus, there is no objective evidence of record to show that SEQ ID No. 1 or SEQ ID NO:2 plays a specific role in metabolic diseases or cancer. Thus, these asserted utilities are not considered "specific" utilities, i.e. they are not specific to the claimed compounds' properties. The specification essentially gives an invitation to experiment wherein the artisan is invited to elaborate a functional use for the disclosed polypeptide.

The instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a credible, specific and

substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696.

8. Claims 3-7, 9, 11, and 12 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

9. The following is a quotation of the first paragraph of 35 U.S.C. 112

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

10. Claims 3-7, 9, 11, and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors to be considered have been summarizes as the quantity of experimentation necessary, the amount of direction or guidance presented, the

presence of absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex Parte Forman*, 230 USPQ 546 (BPAI 1986) and *In re Wands*, 858 F.2d731, 8 USPQ 2d 1400 (Fed. Cir. 1988).

The claims are broadly drawn to an isolated purified polynucleotide that encodes a polypeptide comprising an amino acid sequence selected from SEQ ID No:1, a polynucleotide that encodes a sequence comprising a naturally occurring amino acid that is at least 90% sequence identical to SEQ ID NO:1, a polynucleotide encoding a biologically active fragment of SEQ ID No:1, a polynucleotide encoding an immunogenic fragment of SEQ ID No:1, and polynucleotides linked to a promoter, cells, a polynucleotide of SEQ ID NO:2, a naturally occurring variant at least 90% identical to SEQ ID NO:2, complementary polynucleotides and polynucleotides that are at least 60 contiguous nucleotides of claim 11.

The specification teaches SEQ ID No. 1 (SDHH). SDHH is alleged to be a human serine dehydratase homolog. The properties of SDHH were determined by comparing the sequence of SDHH with rat and human liver dehydratase. The specification only mentions that SDHH has 56.7% identity with human liver dehydratase and also shares a potential casein kinase II phosphorylation site and two potential protein kinase C phosphorylation sites and analysis of these sequences in various libraries shows 48% of these sequences are associated with cancer, 29% are involved in immune response, and 23% are fetal, cell line or proliferating (see pages 14). Besides the sequence comparison, there is no sufficient evidence showing the

relationship of SDHH to human serine dehydratase. A mere factor of similarity of the sequences does not predict the activity of the new protein and even a small difference between sequences could render substantial differences between the activities of the proteins. The specification also fails to teach how to use SDHH as diagnostic tools and therapeutic agents or as pharmaceutical agents. No correlation between SDHH and metabolic diseases and cancer has been established. Thus, undue experimentation would be required to use the instantly claimed polypeptides.

Given the undue experimentation required to use the claimed polynucleotides, it would also require undue experimentation to make and/or use immunogenic portions or biologically active portions of the polypeptides that are encoded by the polynucleotides. Additionally, given the lack of description of the regions of the polypeptides which are definitive of specific antigenic, it would require undue experimentation to obtain immunogenic portions, even if the polypeptides and the polynucleotides which encode them were enabled. Additionally, because there is no evidence identifying the biologically active domain (see below), it would also require undue experimentation to obtain biologically active fragments of SDHH. There is no guidance regarding which portions of the polypeptide are immunogenic, definitive or active. In addition, the specification does not teach any other "naturally occurring" amino acid sequence that is at least 90% identical to SEQ ID NO:1 which would have the activity of SEQ ID NO:1.

Claim 1 is broadly drawn to a polynucleotide which encodes a polypeptide comprising a naturally-occurring amino acid sequence having at least 90% sequence identity to the amino acid sequence of SEQ ID No:1, however, the specification does

not enable any amino acid sequence other than SEQ ID No:1. The specification fails to provide an activity for SEQ ID No:1, therefore, one skilled in the art would not reasonably know how to screen for active naturally occurring sequences that are 90% identical to SEQ ID No:1.

Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, the replacement of a single lysine at position 118 of the acidic fibroblast growth factor by a glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological activity of the protein (see Burgess et al, Journal of Cell Biology Vol 111 November 1990 2129-2138). In transforming growth factor alpha, replacement of aspartic acid at position 47 with asparagine, did not affect biological activity while the replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen (see Lazar et al Molecular and Cellular Biology Mar 1988 Vol 8 No 3 1247-1252).

Replacement of the histidine at position 10 of the B-chain of human insulin with aspartic acid converts the molecule into a superagonist with 5 times the activity of nature human insulin. Schwartz et al, Proc Natl Acad Sci USA Vol 84:6408-6411 (1987). Removal of the amino terminal histidine of glucagon substantially decreases the ability of the molecule to bind to its receptor and activate adenylate cyclase. Lin et al Biochemistry USA Vol 14:1559-1563 (1975). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of the protein.

In addition the clams encompass polynucleotides which encode immunogenic fragments of SEQ ID NO:1. While it would be routine to produce fragments of SEQ ID NO:1 and the fragments would be immunogenic in a specific organism, not all of these fragments would produce an antibody that would bind to the native protein of SEQ ID NO:1. It is well known in the art that fragments that are hydrophobic or buried in the protein would may elicit an immune response, however, these fragments would not be recognized by an antibody when in the native protein because they are not on the surface of the protein. Thus, while one can make antibodies which recognize a fragment of SEQ ID NO:!, the antibody may not recognize the native structure and therefore, would not be useful for methods such as detection of SEQ ID NO:1.

Moreover, the claims encompass polynucleotides which encode biologically active fragments of SEQ ID NO:1, however, the specification does not teach specific regions in the protein which are responsible for its biological activity.

In view of the lack of predictability in the art, lack of guidance, and lack of examples, one skilled in the art would be forced into undue experimentation in order to practice the broadly claimed invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

12. Claims 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Iwahori et al (WO 94/03599, published 2/17/94).

The claims recite an isolated polynucleotide that is complementary to SEQ ID NO:2 and a polynucleotide comprising at least 60 contiguous nucleotides of SEQ ID NO:2.

Iwahori et al teach a polynucleotide sequence, SEQ ID NO:40 (see page 68), which is at least 60 contiguous nucleotides of SEQ ID NO:2 and it would be inherent that the sequence of Iwahori et al contains the complement polynucleotide sequence (see the attached sequence alignment attached to the back of this Office Action, "Db" is the sequence of Iwahori et al and "Qy" is SEQ ID NO:2 of the instant application).

13. Claims 11-12 are rejected under 35 U.S.C. 102(b) as being anticipated by Accession Number AA573827.

The claims have been described supra.

Accession Number AA573827 teaches a polynucleotide that is at least 60 contiguous nucleotides of a polynucleotide that is complementary to SEQ ID NO:2 (see the attached sequence alignment attached to the back of this Office Action, "Db" is the sequence of Accession Number AA573827 and "Qy" is SEQ ID NO:2 of the instant application).

Conclusions

14. No Claims are allowed.

15. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Larry R. Helms, Ph.D, whose telephone number is (703) 306-5879. The examiner can normally be reached on Monday through Friday from 6:30 am to 4:00 pm, with alternate Fridays off. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

16. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center telephone number is (703) 308-4242.

Respectfully,

Larry R. Helms Ph.D.

703-306-5879